APPL. NO.	:	09/357,349
APPLICANTS	:	Geerts, *et al.*
FILED	:	July 14, 1999
TITLE	:	Neurotrophic Growth Factor
TC/AU	:	1647
EXAMINER	:	Sharon L. Turner, Ph.D.
DOCKET NO	:	23887.010200

REQUEST FOR INTERFERENCE PURSUANT TO 37 C.F.R. § 41.202

Sir:

The present Request for Interference is being filed concurrently with a Response to the May 20, 2005 Office Action in the above-identified Application.

No fee is deemed necessary in connection with the filing of this Request. However, if any fee is required, authorization is hereby given to charge of amount of such fee to Greenberg Traurig, LLP Deposit Account No. 50-1561.

(1) Identification of the Patent under 37 C.F.R. § 41.202(a)(1)

Pursuant to 37 C.F.R. § 41.202(a)(1), Applicants request the declaration of an Interference between the above-identified Application and United States Patent No. 6,734,284, issued May 11, 2004, issued to Teit E. Johansen, *et al.* (hereinafter "the Johansen Patent"). A copy of the Johansen Patent is attached hereto as **Exhibit A**. The Johansen Patent purports on its face to be assigned to NsGene A/S, Ballerup (DK).

(2) Proposed Count and Identification of the Claims Corresponding to the Count under 37 C.F.R. § 41.202(a)(2)

Proposed Count 1 is directed to an isolated human neurotrophic polypeptide which includes an open reading frame having the amino acid sequence set forth below, and promotes the survival of a neuronal cell. The following count is proposed:

Count 1:

An isolated polypeptide with neurotrophic activity comprising the following amino acid sequence:

AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLS
LASLLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG.

Claims of the Johansen Patent Correspond to the Count:

Applicants respectfully submit that all nine claims in the Johansen Patent correspond to proposed Count 1.

Claim 1 of the Johansen Patent corresponds to the proposed Count 1. Claim 1 is directed to an isolated neublastin polypeptide with neurotrophic activity, having certain physical characteristics with respect to SEQ ID NO: 2. In Table 1, a Clustal W alignment is provided, showing SEQ ID NO: 2 from the Johansen Patent (a/k/a Neublastin), aligned to the polypeptide sequence of the proposed Count 1. Numbering of SEQ ID NO: 2 in accordance with the scheme given in the Johansen Patent begins at the N-terminal serine as residue 1, and does not include the five deleted residues, (*i.e.*, the glycine residues downstream of the gap are numbered 4 and 5), consistent with the numeration of SEQ ID NO: 2 in the Johansen Patent.

TABLE 1.

CLUSTAL W (1.82) Multiple Sequence Alignment of Neublastin (SEQ ID NO: 2) to Proposed Count 1.

```
Neublastin    ---SGS-----GGAGCRLRSQLVPVRALGLGHRSDELVRFRFCTGSCPRARSPHDLSLAS 52
Count 1       AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60
                  **      *  ***************************** *** ************

Neublastin      LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 105
Count 1         LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
                ******************************************************
```

SEQ ID NO: 2, when numbered as recited in the Johansen Patent, has the following structural properties:

(a) seven conserved cysteine residues at positions 8, 35, 39, 72, 73, 101, and 103;

(b) amino acid residues as follows:

C at position 8, L at position 10, V at position 17, L at position 20, G at position 21, L at position 22, G at position 23, E at position 28, F at position 32, R at position 33, F at position 34, C at position 35, G at position 37, C at position 39, C at position 72, C at position 73, R at position 74, P at position 75, F at position 83, D at position 85, S at position 97, A at position 98, C at position 101 and C at position 103; and

(c) an LGLG repeat, an FRFC motif, a QPCCRP motif, and a SATACGC motif.

As can be seen in Table 1, the sequence provided in the proposed Count 1, if numbered in accordance with SEQ ID NO: 2 (*i.e.,* not counting the 8 additional amino acids at the N-terminus), would have the identical structural properties and numeration recited in claim 1.

Claim 1 also provides that the isolated neublastin polypeptide has neurotrophic activity, which corresponds to the neurotrophic activity recited by the proposed Count 1. Claim 1 also encompasses sequences having at least 90% sequence identity to the sequence set forth in proposed Count 1. As seen in Table 1, the sequence of the proposed Count differs by only 5 amino acids compared to the sequence of amino acids 1-105 recited by claim 1, resulting in greater than 95% identity between the two.

Claims 2-7 of the Johansen Patent are all directed to isolated polypeptides with neurotrophic activity, all having amino acid sequences that fall within the scope of claim 1. Since claims 2-7 are all directly or indirectly dependent on claim 1 and the proposed count corresponds to claim 1 of the Johansen Patent, then the polypeptides covered by claims 2-7 would all fall within the scope of independent claim 1, and accordingly, claims 2-7 all correspond to the proposed count.

Claim 8 of the Johansen Patent is drawn to glycosylated polypeptides of claims 1-7. The priority document for the present application discloses that the amino acid sequence recited in claim 7 can be glycosylated. See, *e.g.,* Figure 1 and discussion thereof at page 13. Furthermore, the advantages of glycosylating neurotrophic polypeptides were well known at the time of filing of the Johansen Patent. For example, see, WO 97/08196 to Johnson *et al.,* published March 6, 1997, which discloses the neurotrophic growth factor neurturin, (shown in the Johansen Patent aligned with SEQ ID NO: 2), in which WO 97/08196 discloses the mature neurotrophic growth factor neurturin is glycosylated. See also, Kotzbauer PT, *et al.;* (1996),

Neurturin, a relative of glial-cell-line-derived neurotrophic factor. Nature. Dec 5;384(6608):467-70, which teaches the same. Likewise see, Lin LF, (1994) Purification and initial characterization of rat B49 glial cell line-derived neurotrophic factor. J. Neurochem. Aug; 63(2):758-68, which teaches that human glial cell line-derived neurotrophic factor (GDNF), is heterogeneously glycosylated, and is a potent neurotrophic factor that exhibits relative specificity for the dopaminergic neurons, and promotes the survival, morphological differentiation, and high-affinity dopamine reuptake of dopaminergic neurons in midbrain cultures, without obvious effects on total neurons or glia and without increasing high-affinity GABA or serotonin reuptake. As before, the Johansen Patent provides an alignment of GDNF with SEQ ID NO: 2. Therefore, the Patentee was aware that protein in this GDNF family are glycosylated, and it would have been an obvious variation of the invention to claim a glycosylated neublastin.

Claim 9 of the Johansen Patent is drawn to pharmaceutical compositions of the polypeptides of claims 1-8. The priority document for the present application discloses that the amino acid sequence recited in claim 7 can be employed in a pharmaceutical composition. See, *e.g.,* pages 1, 6, 10 and 12; and claim 21 as originally filed. Furthermore, the advantages of adding a pharmaceutical carrier to a polypeptide were well known at the time of filing of the Johansen Patent. See, Remington's Pharmaceutical Sciences, 19th Ed., Easton, Pa., Mack Publishing Co., 1995. Therefore a pharmaceutical preparation of neublastin would have been an obvious variation of the invention at the time of filing.

Accordingly, given that broad general knowledge of both glycosylation of neurotrophic factors (and peptides in general) as well as the incorporation of therapeutic peptides with pharmaceutical carriers, available in the art at the filing date of the Johansen Patent, claims 8 and 9 would have been obvious in light of polypeptide sequences in the proposed Count in view of the general knowledge on peptide glycosylation and pharmaceutical carriers known in the art.

Claims of the Present Patent Application Correspond to the Count:

Proposed Count 1 is essentially identical to pending claim 7, as amended in the concurrently-filed Amendment and Response. SEQ ID NO: 3 is identical to the polypeptide sequence recited in the proposed Count 1. Upon entry of the concurrently-filed Amendment and Response, claim 7 will be the only pending claim.

(3) Claim chart of claims Corresponding to the Count under 37 C.F.R. § 41.202(a)(3)

As required under 37 C.F.R. § 41.202(a)(3), a claim chart is provided below to compare at least one claim of the Johansen Patent with at least one claim of the present Application that correspond to proposed Count 1.

CLAIMS FROM THE JOHANSEN PATENT	CLAIMS FROM THE PRESENT APPLICATION
Claim 1. An isolated neublastin polypeptide with neurotrophic activity comprising the following:	**Claim 7.** An isolated human neurotrophic polypeptide comprising
(a) seven conserved cysteine residues at positions 8, 35, 39, 72, 73, 101, and 103 when numbered in accordance with SEQ ID NO. 2; (b) amino acid residues as follows: C at position 8, L at position 10, V at position 17, L at position 20, G at position 21, L at position 22, G at position 23, E at position 28, F at position 32, R at position 33, F at position 34, C at position 35, G at position 37, C at position 39, C at position 72, C at position 73, R at position 74, P at position 75, F at position 83, D at position 85, S at position 97, A at position 98, C at position 101 and C at position 103, each when numbered in accordance with SEQ ID NO. 2; (c) an LGLG repeat, an FRFC motif, a QPCCRP motif, and a SATACGC motif; and (d) an amino acid sequence comprising at least 90% sequence identity to AA_1-AA_{105} of SEQ ID NO. 2.	the amino acid sequence of SEQ ID NO: 3.

For comparison purposes, a Clustal W sequence alignment of SEQ ID NO: 2 in the claims of the Johansen Patent (designated as Neublastin by the Patentee) and SEQ ID NO: 3 in claim 7 of the present Application (designated as Enovin by the Applicant) is provided below in Table 2. Conserved residues are indicated by a "*".

TABLE 2

CLUSTAL W (1.82) Multiple Sequence Alignment of Neublastin (SEQ ID NO: 2) to Enovin (SEQ ID NO: 3)

```
Neublastin    ---SGS-----GGAGCRLRSQLVPVRALGLGHRSDELVRFRFCTGSCPRARSPHDLSLAS 52
Enovin        AGGPGSRARAAGARGCRLRSQLVPVRALGLGHRSDELVRFRFCSGSCRRARSPHDLSLAS 60
                  **      *  ****************************** *** ************

Neublastin      LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 105
Enovin          LLGAGALRPPPGSRPVSQPCCRPTRYEAVSFMDVNSTWRTVDRLSATACGCLG 113
                ******************************************************
```

As can be seen by the sequence alignment above, SEQ ID NO: 3 of the present Application, when numbered in accordance with SEQ ID NO: 2 in claim 1 of the Johansen Patent, also has (a) seven conserved cysteine residues, which correspond to those found at positions 8, 35, 39, 72, 73, 101, and 103 of SEQ ID NO: 2 of the Johansen Patent; (b) corresponding amino acids to the C at position 8, L at position 10, V at position 17, L at position 20, G at position 21, L at position 22, G at position 23, E at position 28, F at position 32, R at position 33, F at position 34, C at position 35, G at position 37, C at position 39, C at position 72, C at position 73, R at position 74, P at position 75, F at position 83, D at position 85, S at position 97, A at position 98, C at position 101 and C at position 103, of SEQ ID NO: 2 of the Johansen Patent; and (c) an LGLG repeat, an FRFC motif, a QPCCRP motif, and a SATACGC motif. Furthermore, SEQ ID NO: 3 of the present Application has 100 amino acids identical to AA_1-AA_{105} of the open reading frame of SEQ ID NO: 2 of the Johansen Patent, representing greater than 90% identity (95.2%), as recited in element (d) of claim 1 of the Johansen Patent and in the proposed Count 1.

Accordingly, claim 7 of the present Application, which is drawn to an isolated neurotrophic polypeptide with neurotrophic activity comprising the amino acid sequence of SEQ ID NO: 3 would have anticipated claim 1 of the Johansen Patent since SEQ ID NO: 3 has the seven conserved cysteine residues of element (a), the corresponding amino acids of element (b), the repeat and motifs of element (c) of the Johansen Patent, and greater than 90% identity (95.2%) with SEQ ID NO: 2 of the Johansen Patent recited in element (d).

(4) Applicants Prevail on Priority

Applicants will prevail on priority, as required under 37 C.F.R. § 41.202(a)(4).

The Johansen Patent claims priority to four U.S. applications and three Danish applications: it is a divisional application of USSN 09/347,613 (now U.S. Pat. No. 6,593,133), filed Jul. 2, 1999, which claims the benefit of USSN 60/103,908, filed Oct. 13, 1998; DK 1998 01265, filed Oct. 6, 1998; USSN 60/097,774, filed Aug. 25, 1998; DK 1998 01048, filed Aug. 19, 1998; USSN 60/092,229, filed Jul. 9, 1998; and DK 1998 00904, filed July 6, 1998.

In the present Application, Applicants claim the earliest priority to UK 9815283.8 filed July 14, 1998. The disclosure of the earliest priority application includes isolated polynucleotides encoding the functional Enovin mature polypeptide (*i.e.,* the sequence recited in claim 7), immature polypeptide, and functional variants thereof. The earliest priority date of the Johansen Patent is July 6, 1998. Applicants respectfully submit that the polynucleotide and amino acid sequences provided in the earliest priority document for the Johansen Patent differ from the sequence recited in claim 7 in several ways, including but not limited to, (i) that it lacks 14 N-terminal amino acids; (ii) that it does not include the RAAR furin cleavage site for prodomain cleavage and activation; and (iii) that it includes at least one point mutation (R158P). Thus, Applicants respectfully submit that the amino acid sequence disclosed in the earliest priority document for Johanssen et al. was not the sequence recited in claim 7, nor functionally equivalent to the sequence recited in claim 7. A sequence corresponding to that recited in claim 7 was introduced in a later-filed priority application for the Johansen Patent. For example, the first presentation of a sequence without the point mutation (R158P) was included in the application DK 1998 01048, filed Aug. 19, 1998. Accordingly, Applicants respectfully submit that Applicants' priority patent application (i.e., UK 9815283.8, filed July 14, 1998) contains a sequence corresponding to the sequence recited in claim 7 and represents an earlier constructive reduction to practice of said sequence than the Johansen Patent.

In addition, in the November 17, 2004 Amendment and Response, Applicants filed a Declaration under 37 C.F.R. § 1.131 ("Declaration"), which demonstrates that Applicants were in possession of the amino acid sequence recited in claim 7 prior to the earliest filing date of the Johansen patent. A copy of the Declaration is attached for the Office's review. For the reasons discussed above, Applicants respectfully submit that the present invention will prevail on priority.

(5) Support for Added or Amended Claims under 37 C.F.R. § 41.202(a)(5)

Pursuant to 37 C.F.R. § 41.202(a)(5), support for amended claims 7-9 of the present Application is provided in the chart below.

AMENDED CLAIMS	SUPPORT IN DISCLOSURE FOR AMENDMENTS
Claim 7. An isolated human neurotrophic polypeptide	Page 4, line 31 through page 5, line 8; page 11, lines 14-20; page 14, lines, 1-8, and 15-31.
comprising the amino acid sequence of SEQ ID NO: 3.	SEQ ID NO: 3; FIG. 1.

(6) Support for Constructive Reduction to Practice under 37 C.F.R. § 41.202(a)(6)

Pursuant to 37 C.F.R. § 41.202(a)(6), support for each constructive reduction to practice is provided in the chart below.

AMENDED CLAIMS	SUPPORT IN DISCLOSURE FOR EACH RTP
Claim 7. An isolated human neurotrophic polypeptide	**USSN 09/357,349**: Page 4, lines 27-end; FIG. 1. **USSN 09/327,668**: Page 4, lines 27-end; FIG. 1. **USSN 09/248,772:** Page 4, lines 27-end; FIG. 1. **UK 9815283.8**: Page 4, lines 15-23; FIG. 1.
comprising the amino acid sequence of SEQ ID NO: 3,	**USSN 09/357,349**: Page 25, line 18 through page 26, line 2; FIG. 1. **USSN 09/327,668**: Page 20, line 24 through page 21, line 6; FIG. 1. **USSN 09/248,772**: Page 15, lines 9-26; FIG. 1. **UK 9815283.8**: Page 12, lines 14-31; FIG. 1.

Applicants respectfully submit that the chart above clearly demonstrates that the present Application and each of the priority applications provide a constructive reduction to practice within the scope of the interfering subject matter of proposed Count 1.

CONCLUSION

Applicants respectfully request that an interference be declared employing Count 1 with claims 1-9 of the Johansen Patent and claim 7 of the present Application. Such action is respectfully requested.

Respectfully submitted,

Dated: October 19, 2005

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10-20-05

AF/1647 (BSH)

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission

Application Number	09/357,349
Filing Date	July 14, 1999
First Named Inventor	Geerts, et al.
Art Unit	1647
Examiner Name	Turner, S.
Attorney Docket Number	23887.010200

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [ ] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
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- [ ] CD, Number of CD(s) _____
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- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
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Remarks

Request for Interference Pursuant to 37 CFR 41.202 with two exhibits
Information Disclosure Statement with USPTO 1449 form
Three (3) cited references
Certificate of Express Mail EV 570 903 173 US
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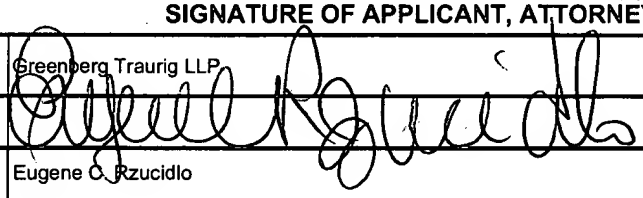
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Greenberg Traurig LLP		
Signature			
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Date	October 19, 2005	Reg. No.	31,900

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

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Typed or printed name		Date	

PTO/SB/17 (12-04v2)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT	($)	580

Complete if Known	
Application Number	09/357,349
Filing Date	July 14, 1999
First Named Inventor	Geerts, et al.
Examiner Name	Turner, S.
Art Unit	1647
Attorney Docket No.	23887.010200

METHOD OF PAYMENT (check all that apply)

☐ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 50-1561 Deposit Account Name: Greenberg Traurig LLP

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

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FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	$0
Design	200	100	100	50	130	65	$0
Plant	200	100	300	150	160	80	$0
Reissue	300	150	500	250	600	300	$0
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	- 20 or HP =	0	x	$0	=	$0

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims		Extra Claims		Fee ($)		Fee Paid ($)
_____	- 3 or HP =	0	x	$0	=	$0

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($)	Multiple Dependent Claims Fee Paid ($)
$0	$0

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets		Extra Sheets		Number of each additional 50 or fraction thereof		Fee ($)		Fee Paid ($)
0	- 100 =	0	/ 50 =	0.0 (round **up** to a whole number)	x	$250	=	$0

4. OTHER FEE(S)

	Fees Paid ($)
Non-English Specification, $130 fee (no small entity discount)	
Other (e.g. late filing surcharge): extension of time and petition to consider IDS	$580

SUBMITTED BY

Signature		Registration No. (Attorney/Agent) 31,900	Telephone 212 801 2146
Name (Print/Type)	Eugene C. Rzucidlo		Date October 19, 2005

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): Geerts, et al.			Docket Number 23887.010200
Serial No. 09/357,349	Filing Date July 14, 1999	Examiner Turner, S.	Group Art Unit 1647

Invention: NEUROTROPHIC GROWTH FACTOR

I hereby certify that the following correspondence:

1) Transmittal Form (1 page);
2) Fee Transmittal Form (1 page) in duplicate with authorization to charge deposit account $580;
3) Amendment and Response under 37 CFR 1.116
4) Request for Interference Pursuant to 37 CFR 41.202 with two exhibits
5) Information Disclosure Statement with USPTO 1449 form
6) Three (3) cited references
7) postcard receipt

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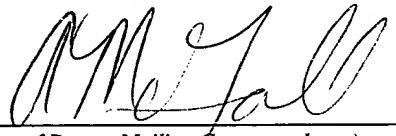

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